REMARKS

I. Status Summary

Claims 1-5, 8, and 18-22 are pending in the instant application and have been examined.

Claims 1-4 have been rejected under 35 U.S.C. § 102(a) as being anticipated by Lapeyre *et al.* (WO 95/00178; hereinafter "Lapeyre").

Claims 1-5, 8, and 18-22 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gunzburg *et al.* (364 *Nature* 154-158, 1993; hereinafter "Gunzburg"), U.S. Patent No. 5,658,775 (hereinafter "the '775 Patent"), and U.S. Patent No. 5,219,740 (hereinafter "the '740 Patent").

Claims 1-4 and 18-21 have been canceled. Claims 5 and 8 have been amended. Support for the amendments can be found throughout the specification as filed, including particularly in the claims as originally filed. Additional support can be found in Figure 5 (vector encoding a therapeutic gene and a Sag peptide, with a heterologous promoter in between, and the 3' U3 at least partially replaced with a tissue-specific promoter).

New claims 23-25 have been added. Support for the new claims can be found throughout the specification as filed, including particularly in the claims as originally filed. Additional support can be found on page 11, line 24, through page 12, line 3 (retrovirus vector with Sag coding sequence inserted into the 3' U3 deletion) and in Figure 5 (promoter converting vector with both the therapeutic gene and the Sag coding sequence in the body of the vector, with the therapeutic gene being regulated by the promoter inserted into the 3' U3 deletion after promoter conversion and the Sag coding sequence being regulated by a second operably linked promoter).

No new matter has been added by the amendments to the claims or the addition of the new claims. Reconsideration of the application as amended and based on the remarks set forth herein below is respectfully requested.

II. Response to the Anticipation Rejection

Claims 1-4 have been rejected under 35 U.S.C. § 102(a) as being anticipated by Lapeyre. According to the Patent Office, Lapeyre discloses a recombinant vector comprising a nucleotide sequence capable of infecting and directing the expression of a coding sequence and a sequence encoding a peptide with Sag activity; a sequence encoding a non-therapeutic peptide present in the vector along with the Sag gene cassette; and the expression of a therapeutic peptide in addition to Sag.

While applicants do not necessarily agree with the Patent Office's contentions regarding Lapeyre and claims 1-4, in an effort to facilitate the prosecution of the other pending claims applicants have canceled claims 1-4. Accordingly, applicants respectfully submit that the rejection of claims 1-4 under 35 U.S.C. § 102(a) as being anticipated by Lapeyre has been rendered moot, and respectfully request that the rejection be withdrawn at this time.

III. Response to the Obviousness Rejection

Claims 1-5, 8, and 18-22 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gunzburg, the '775 Patent, and the '740 Patent. According to the Patent Office, the claims are drawn to a recombinant replication-defective retroviral vector capable of promoter conversion comprising a 5' LTR comprising the structure U3-R-U5, a sequence encoding a peptide with Sag activity, and a 3' LTR comprising a completely or partially deleted U3 region that is replaced by a promoter expressing heterologous DNA sequences, followed by R-U5. The Patent Office further asserts that Gunzburg disclose a promoter located in the U3 region of the 5' MMTV LTR and splice donor/acceptor sites expressing an endogenous Sag and that Sag expression results in T-cell proliferation.

The Patent Office concedes that Gunzburg do not teach a replication-defective retrovirus comprising a completely or partially deleted U3 region that is replaced by a promoter expressing heterologous DNA sequences followed by R-U3 or a host cell comprising the retroviral construct. The Patent Office asserts, however, that this deficiency is cured by the '775 Patent, which is asserted to disclose a murine retroviral

vector comprising a 5' LTR and a completely or partially deleted U3 region of the 3' LTR replaced by a heterologous promoter and a DNA sequence followed by R-U5. The Patent Office further asserts that the '775 Patent discloses self-inactivating vectors (SIN), which expresses a gene between the 5' LTR and the 3' LTR, and a retroviral vector expressing a non-therapeutic gene. The Patent Office thus contends that one of ordinary skill in the art would have been motivated to (a) replace at least a portion of the 3' LTR U3 region with a heterologous promoter and DNA sequence as taught by the '775 Patent, into the MMTV of Gunzburg to generate self-inactivating vectors and introduce therapeutic genes to a host; and (b) to delete at least a portion of the 3' LTR region within the MMTV of Gunzburg to disable activation of cellular oncogenes. The Patent Office asserts that one of ordinary skill in the art would have had a reasonable expectation of success in producing an MMTV expressing Sag and 3' LTR U3 region comprising a heterologous promoter and DNA sequence because Gunzburg specifically identify the nucleotides and splice sites required for Sag expression and the '775 Patent teach that SIN vectors are generated by deleting or replacing any portion of the 3' LTR region.

After careful consideration of the rejection and the Patent Office's bases therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully submit that claims 1-4 and 18-21 have been canceled, and thus the instant rejection is moot as to these claims. While applicants respectfully disagree with the Patent Office's assertions concerning claims 1-4 and 18-21, these claims are being canceled to facilitate prosecution of the remaining claims. Applicants reserve the right to file one or more continuing applications directed to the subject matter of the instantly canceled claims.

Continuing with the instant rejection, the Patent Office asserts *inter alia* that one of ordinary skill in the art would have been motivated to replace at least a portion of the 3' LTR U3 region with a heterologous promoter and DNA sequence as taught by the '775 Patent, into the MMTV of Gunzburg to generate self-inactivating vectors and introduce therapeutic genes to a host. Applicants respectfully submit, however, that

the retroviral vectors as recited in claim 5 are not characterized by the replacement of a portion of the 3' LTR U3 region with a heterologous promoter and DNA sequence as taught by the '775 Patent; and are not SIN vectors. Applicants respectfully submit that SIN vectors are vectors that have 3' LTRs wherein the promoters and/or regulatory sequences are either deleted, disabled (for example, by mutation), or linked to coding sequences such that when the retrovirus reverse transcribes its genome, the duplication of the sequences present in the 3' U3 region results in a retrovirus that cannot transcribe any sequences present in the body of the vector.

Thus, applicants respectfully submit that the vectors disclosed in the '775 Patent are SIN vectors, and that the vectors of claim 5, on the other hand, are not SIN vectors. Rather, the claimed vectors are designed specifically to employ regulatory elements present within the modified 3' LTR U3 sequence to regulate the expression of coding sequences present within the body of the vector after promoter conversion. Claim 5 has been amended to reflect this relationship. Accordingly, applicants respectfully submit that the cited combination does not disclose or suggest the vectors of claim 5.

In fact, the '775 Patent teaches against the construction of retroviral vectors containing functional regulatory elements in the 3' U3 region, because unless these regulatory elements are operably linked to coding sequences also present within the 3' LTR, a SIN vector does not result. Applicants respectfully submit that the vectors claimed in claim 5 do not have such coding sequences operably linked to the regulatory elements and/or promoter located with the 3' U3, and as such, are not SIN vectors. Since the motivation asserted by the Patent Office for combining the '775 Patent with Gunzburg relies on the creation of a SIN vector, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of obviousness of claim 5 over the combination of Gunzburg and the '775 Patent.

Applicants further respectfully submit that the Patent Office's assertion that the '775 Patent teaches "self-inactivating vectors (SIN), which express a gene between the 5' LTR and the 3' LTR" (Official Action at page 5) is not relevant to the subject matter of claim 5. As described in the '775 Patent and more clearly shown in Figure

2C, the only mechanism by which a SIN vector can express a gene within the body of the vector is if the gene is operably linked to a promoter also within the body of the vector. This is clear from the nature of the SIN vector, in which the regulatory elements normally found within the 3' LTR are inactivated. Upon entry of a SIN vector into a cell, reverse transcription results in the duplication of the 3' U3 sequence (*i.e.* the defective promoter) upstream of the body of the vector. Thus, it is only when the body of the vector itself also contains a promoter that genes present within the body of a SIN vector can be expressed.

This is in contrast to the instantly claimed vectors. As recited in claim 5, for example, the claimed vectors are recombinant retroviral vectors that are characterized *inter alia* by (a) a complete 5' LTR; (b) a coding sequence present in the body of the vector encoding a therapeutic peptide; (c) a SAG gene also within the body of the vector, optionally operably linked to a promoter; and (d) a modified 3' LTR, wherein the modification includes the replacement of part or all of the U3 region with non-coding sequences (*e.g.* regulatory elements and/or a promoter). The recombinant retroviral vector is designed to undergo promoter conversion, whereby the heterologous regulatory elements and/or promoter present in the 3' LTR is placed in operable linkage with the coding sequence present in the body of the vector encoding the therapeutic peptide after the vector enters a cell. Thus, applicants respectfully submit that the design of the vector ensures that the coding sequence encoding the therapeutic peptide is expressed only after the promoter conversion event.

Thus, applicants respectfully submit that the method of operation of the vectors disclosed in the '775 Patent is entirely different than the method of operation of the claimed vectors. As a result, applicants respectfully submit that the combination of Gunzburg and the '775 Patent does not support a rejection of claim 5.

Continuing with the instant rejection, applicants further respectfully submit that the cited combination does not support a rejection under 35 U.S.C. § 103(a) because the cited combination does not disclose or suggest each and every element of the claims. Claim 5 has been amended to recite a recombinant retroviral vector which is

capable of undergoing promoter conversion and is replication-defective comprising, in a 5' to 3' direction:

a) a 5' long terminal repeat region comprising the structure U3-R-U5:

b) a first coding sequence encoding a therapeutic peptide;

c) a second coding sequence encoding a peptide with Sag activity operably linked to a promoter, wherein the promoter is active in at least one of B cells and T cells, and

d) a 3' long terminal repeat region comprising a completely or partially deleted U3 region followed by the R and U5 region,

wherein said completely or partially deleted U3 region is replaced by a polylinker sequence comprising at least one unique restriction site into which is inserted one or more non-coding sequences selected from regulatory elements and promoters, which regulate expression of the first coding sequence after promoter conversion.

Accordingly, applicants respectfully submit that even if the cited references were combined as suggested by the Patent Office, the references would not disclose or suggest a retroviral vector characterized by (a) a fully functional 5' LTR; (b) a coding sequence encoding a therapeutic peptide; (c) a coding sequence encoding a peptide with Sag activity operably linked to a B cell- and/or T cell-specific promoter; and (d) a recombinant 3' LTR containing a deletion of U3, into which has been inserted a polylinker containing one or more non-coding sequences that are designed to regulate the transcription of the coding sequence encoding the therapeutic peptide after promoter conversion. Stated another way, applicants respectfully submit that the cited combination does not disclose or suggest two coding sequences present within the body of the vector, one encoding a therapeutic peptide that is expressed in target cells from a heterologous promoter inserted into a '3 U3 deletion, and the other encoding a peptide with Sag activity that is expressed via a B cell- and/or T cell-specific promoter to which it is operably linked (*i.e.* that is also present within the body of the vector).

Thus, applicants respectfully submit that the combination of Gunzburg and the '775 Patent does not support a rejection of claim 5 or the claims that depend from claim 5.

And finally, the Patent Office asserts that the motivation to combine the cited references would have been to "generate self-inactivating vectors and introduce therapeutic genes to a host" or alternatively to "delete at least a portion of the 3' LTR U3 region within the MMTV of Gunzburg et al. to disable activation of cellular oncogenes". Official Action at page 5. With regard to the first asserted motivation, applicants respectfully submit that the vectors of claim 5 are not self-inactivating, and thus the first asserted motivation is clearly unsupported. Furthermore, with regard to the second asserted motivation, the deletion of portions of the 3' U3 will only disable activation of cellular oncogenes if the deletion results in the absence of promoter activity within the U3. Alternatively, if a promoter remains or is inserted into the deletion, an operably linked coding sequence must be also inserted.

Applicants respectfully submit that neither of these approaches is taken by the vectors of claim 5. Rather, the claimed vectors replace the promoters normally found in the 3' U3 with functional promoters and/or regulatory elements of interest (*e.g.* tissue-specific promoters of interest), which after promoter conversion direct expression of coding sequences present within the body of the vector. As such, the claimed vectors have functional promoters in the 3' U3 region, and thus would not be expected to "disable activation of cellular oncogenes" as suggested by the Patent Office. As a result, applicants respectfully submit that even if one of ordinary skill in the art were motivated as suggested by the Patent Office, such a motivation would not result in the skilled artisan arriving at the vector of claim 5.

Accordingly, applicants respectfully request that the instant rejection under 35 U.S.C. § 103(a) of claim 5 over the combination of Gunzburg and the '775 Patent be withdrawn. Claims 8 and 22 depends from claim 5, and thus claims 8 and 22 are believed to also be patentably distinguished from the cited combination. Thus, applicants respectfully request that the instant rejection of claims 5, 8, and 22 be withdrawn, and the claims allowed at this time.

IV. Discussion of the New Claims

New claims 23-25 have been added. Support for the new claims can be found throughout the specification as filed, including particularly in the claims as originally filed. Additional support can be found on page 11, line 24, through page 12, line 3, and in Figure 5.

Since new claims 23-25 all depend directly or indirectly from patentably distinguished claim 5, applicants respectfully submit that new claims 23-25 are also distinguished from the cited references for the reasons set forth hereinabove with regard to the pending claims. According, applicants respectfully submit that the new claims are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

CONCLUSIONS

In light of the above amendments and remarks, applicants respectfully submit that claims 5, 8, and 22-27 are in condition for allowance at this time, and respectfully solicit a Notice of Allowance to that effect.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

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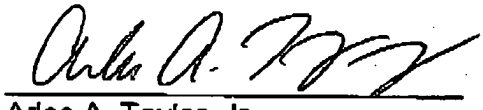
DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
JENKINS, WILSON & TAYLOR, P.A.

Date: 12/13/2004 By: 
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